REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1, 5 and 13 have been amended to incorporate the limitations of claims 21-40 therein. Claims 21-40 have accordingly been cancelled. These amendments are effected to more particularly point out and distinctly claim the subject matter of this invention as defined in the specification. The wording of the subject matter of claims 21-40 has also been clarified in better conformance with U.S. practice and English idiom. The amendments to claims 1, 5 and 13 are supported by cancelled claims 21-40, by page 3, lines 11-18, and by the paragraph bridging pages 11-12 of the specification.

Furthermore, claims 41-60 have been cancelled without prejudice and rewritten as new claims 63-82. The wording of these claims corresponds to the amendments effected to claims 1, 5 and 13, except that the dissolution percentage has been changed from 50% to 80%, which is supported by cancelled claims 41-60.

Turning to the Official Action, claims 1 and 5 were rejected under 35 USC 102 as being anticipated by Negoro et al. (U.S. Patent No. 5,258,382). This ground of rejection is deemed to be overcome by the foregoing amendments. The cited reference fails to disclose a composition which, when compressed into a tablet, has a dissolution percentage of AS-3201 from the tablet of 50% or more within 15 minutes as measured by the Paddle method.

Further, it is respectfully submitted that such distinguishing characteristic of the claimed composition is not inherent in the teachings of the cited reference. In order to rely upon a cited reference as teaching an inherent claimed feature, the claimed feature must be necessarily present in the teachings of the reference, not merely a possibility of being present. There is no teaching or suggestion in the reference which would lead to a conclusion that the composition of the reference necessarily possesses the dissolution rate of the claimed invention. Accordingly, it is respectfully submitted that it would not be proper under PTO practice to take the position that the specified dissolution rate of the claimed composition is inherently taught by the cited reference.

Furthermore, it is respectfully submitted that the cited reference fails to teach a composition comprising a micronized AS-3201 according to the claimed invention. Micronized AS-3201 means powers of AS-3201 having a mean particle size of less than about 20 μm. See page 3, lines 3-4 of the specification. The present invention was based on a discovery that micronized AS-3201 has excellent bioavailability, in comparison with non-micronized AS-3201. See page 2, lines 8-22 of the specification.

Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 1-60 were further rejected under 35 USC 103 as being unpatentable over Negoro et al. in view of Bavitz et al. (U.S. Patent No. 4,910,022). This ground of rejection is also respectfully traversed.

Bavitz et al. disclose in the abstract and specification merely "tablets having a relatively high dose of drug in a relatively small size useful for gaining patient compliance" but never teach a micronized active substance, that is, "a pharmaceutical composition comprising powders of the active substance having a mean particle size of less than about 20 μm" according to the present invention.

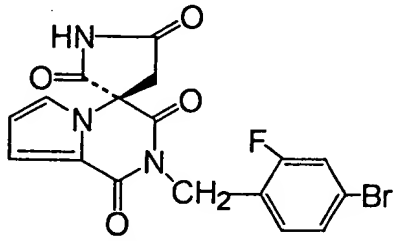
The "sieving" in Bavitz et al. pointed out by the Examiner is a standard procedure in the steps of preparing a pharmaceutical composition, which is done for the purpose of sieving the agglomerates included in granules which are produced in the step of mixing and granulating of the active substance and pharmaceutical excipients or carriers, which step is clearly distinguished from the micronization step in the present invention.

Bavitz et al. disclose a general procedure for preparing tablets of the subject of their invention (the desired lubricated granular tablet formulation), which comprises 9 steps (cf. Bavitz et al., U.S. Patent 4,910,022, col. 3, line 62 - col. 4, line 13). In said procedure, screens (sieves) are used in Step (4), Step (6) and Step (8) where the sieve openings have a size of 1.7-2.4 mm, 0.55-0.65 mm and 0.25 mm, respectively.

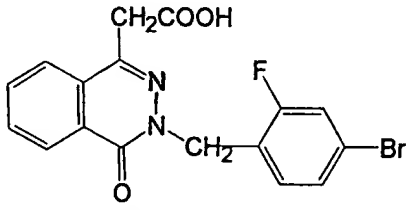
Moreover, in Examples I and II of Bavitz et al., there are used a No. 30 sieve (0.59 mm sieve opening) in step (1), a No. 10 screen (2.00 mm sieve opening) in Step (4), a No. 20 sieve

(0.84 mm sieve opening) in Step (6), and a No. 60 screen (0.25 mm sieve opening) in Step (8), which are all more than 0.25 mm, which are clearly different from the mean particle size of the micronized AS-3201 of the present invention, i.e. less than about 20 μm (i.e. less than about 0.02 mm).

It should also be noted that the phthalazineacetic acid compound used in Bavitz et al. is clearly different from the active ingredient of the present invention. The chemical structure of AS-3201 and the reference compound are shown below.



AS-3201



Phthalazineacetic acid compound

Moreover, the tablets prepared in Bavitz et al. are also clearly different from the pharmaceutical composition of the present invention in the ratio of the active ingredient and excipients to the total weight of the composition as is shown in the following table.

	Bavitz et al.	The present invention	
		Lower content	Higher content
Active ingredient	83-88%	0.5-5%	5-25%
Diluent	8-20%	51-93.8%	16-84.3%
Disintegrator	1-4%	5-35%	10-50%
Binder	1-4%	0.5-5%	0.5-5%
Lubricant	0.5-2%	0.2-4%	0.2-4%

As is seen from the table, the tablets of Bavitz et al. have a very large content of the active ingredient and have a very slight amount of disintegrator (in Bavitz et al. any specific design is given for the preparation of the tablets). Nevertheless, as is pointed out by the Examiner, the tablets have the appropriate physicochemical properties for efficient and effective utilization of the

drug such as rapid disintegration and dissolution, which will probably be owing to the higher solubility of the active ingredient: phthalazineacetic acid compound.

Thus, even though Bavitz et al. disclose that the phthalazineacetic acid compound exhibits an aldose reductase inhibitory activity as like as AS-3201 of the present invention, the present invention would never be motivated merely by such a disclosure of Bavitz et al.

On the other hand, Negoro et al. disclose a method for a specific tablet of AS-3201 in Example 28 (cf. Negoro et al., U.S. Patent 5,258,382, col. 30) but do not disclose or even suggest any properties which should be known for preparing the specific AS-3201-containing pharmaceutical compositions of the present invention. (Please note that the Examiner referred to fine granules in Example 29 of Negoro et al., but it would be more suitable to refer to Example 28, because Bavitz et al. disclose only tablets and further the examples of the present invention are all concerned with tablets).

As is disclosed in the present description, page 2, lines 8-22, the present inventors have found that when AS-3201-containing pharmaceutical compositions prepared by using AS-3201 crystals as disclosed in Negoro et al. are administered, the plasma concentration of the active ingredient, AS-3201, varies widely among the individuals. This is due to the extremely low water-solubility of said substance in the range of low pH to the extent of several μg/ml. Hence the inventors sought to solve the problem of finding a AS-3201-containing pharmaceutical composition having a good bioavailability.

Under the above technical circumstances, the present inventors studied means for micronizing AS-3201 crystals suitable for preparing the desired pharmaceutical composition and have succeeded in preparation of a AS-3201-containing pharmaceutical composition which has extremely improved dissolving properties and superior bioavailability in comparison with a composition prepared by using non-micronized AS-3201 crystals. This is clear from the comparison of the products of Examples and Reference Examples. See Experiment on pages 11-12 of the present description, the results of which are shown in Fig. 1.

For example, as is shown in Fig. 1, the AS-3201-containing pharmaceutical compositions prepared by using micronized AS-3201 having an average particle size of about 1.5 μm or about

10 μm showed about 7.3 times or 4.0 times higher dissolution rate for 15 minutes in comparison with pharmaceutical compositions prepared by using non-micronized AS-3201 crystals having an average particle size of about 87 μm.

As is clear from the above explanation, the present invention is well distinguished from the inventions disclosed in the cited Negoro et al. and Bavitz et al. references and would not be obvious even by combination of them. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Lastly, claims 61 and 62 were rejected under 35 USC 103 as being unpatentable over the combined teachings of Negoro et al. and Bavitz et al., in further view of Ikeda et al. (U.S. Patent No. 5,952,356).

Initially, it is noted that claims 61 and 62 are dependent upon claim 1. The rejection of claim 1 under 35 USC 102 and 35 USC 103 has been overcome, for the reasons described above. Accordingly, the rejection of claims 61 and 62 should be overcome.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

In view of the foregoing, favorable reconsideration and allowance is respectfully solicited.

Respectfully submitted,

Mamoru OHASHI et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
January 22, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended)** A fast-dissolving pharmaceutical composition comprising micronized (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter[,] referred to as "AS-3201"),

wherein when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method, 50% or more of the AS-3201 in the tablet is dissolved within 15 minutes from the start of the method.

5. **(Amended)** A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of about 0.5% by weight - 5% by weight, a diluent in a ratio of about 51% by weight - about 93.8% by weight, a disintegrator in a ratio of about 5% by weight - about 35% by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2% by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein when said composition is compressed into a tablet and a dissolution percentage of AS-3201 from the tablet is measured according to the Paddle method, 50% or more of the AS-3201 in the tablet is dissolved within 15 minutes from the start of the method.

13. **(Amended)** A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of more than 5% by weight and less than about 25% by weight, a diluent in a ratio of about 16% by weight - about 84-3% by weight, a disintegrator in a ratio of about 10% by weight - about 50 % by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein when said composition is compressed into a tablet and a dissolution rate of AS-3201 from the tablet is measured according to the Paddle method, 50% or more of the AS-3201 in the tablet is dissolved within 15 minutes from the start of the method.